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Therapeutic Effect of Dienogest in Patients with Chocolate Cysts

Hiroaki Takagi*, Tsukasa Yamanouchi, Yoshihiko Saeki, Sumire Shimada, Emi Takata, Jinichi Sakamoto, Satoko Fujita, Masahiro Takakura, Toshiyuki Sasagawa

Department of Obstetrics and Gynecology, Kanazawa Medical University

Abstract: Objective: Surgical treatment to remove chocolate cysts requires careful consideration when women desire fertility preservation. Thus, we investigated the effectiveness of conservative dienogest (DNG) treatment in patients with chocolate cysts.
Materials and Methods: Forty Japanese patients with chocolate cysts who were treated with DNG were analyzed. We analyzed the ovarian cyst diameter and the reduction rate after 6 months or more of DNG treatment and compared the group that exhibited a complete (CR) or partial response (PR) after DNG treatment with the group that did not experience ovarian cyst reduction.
Results: The reduction rate was the highest among no greater than 40-mm-wide ovaries, and the effect of DNG decreased when ovaries were 60-70 mm wide. The Spearman correlation coefficient for the association between the ovarian cyst diameter and the reduction rate was $r = -0.478$, $P < 0.01$, which indicates a moderate negative correlation. A significant difference was observed in the diameter of ovarian cysts between the group that achieved PR after DNG treatment and the group that did not experience a reduction in ovarian cyst diameter (48.1 ± 13.4 vs 79.6 ± 33.8 mm, $P < 0.001$). The area under the receiver operating characteristic (ROC) curve was 0.816. For the optimal ovarian cyst diameter, the cutoff value was set at 55.5 mm.
Conclusion: Long-term preservation therapy consisting of DNG should be considered in patients with chocolate cysts <60 mm to achieve PR.

Key Words: endometriosis, chocolate cyst, dienogest, ovarian cyst reduction rate, receiver operating characteristic curve

Introduction

Endometriosis is an estrogen-dependent chronic inflammatory disorder that requires a life-long management plan. Approximately 10% of reproductive-age women are affected by endometriosis (1). Endometriosis affects many organs and structures, including the ovary, fallopian tubes, pelvic serosa, rectum, retroperitoneal structures (e.g., the ureters), and more remote organs such as the lungs. However, the ovaries are the most frequently affected organs. Ovarian endometriosis typically presents as an ovarian cyst containing old blood, which is referred to as a chocolate cyst or an endometrioma. Chocolate cysts are diagnosed in approximately 17%-44% of women with endometriosis (2). In addition, the Japanese Shizuoka Cohort Research Program reported that approximately 0.72% of patients with chocolate cysts ultimately develop ovarian cancer (3). Comprehensive and early surgical intervention after chocolate cyst rupture can prevent ovarian malignancies, reduce the effects of cyst fluids, prevent adhesions, and preserve fertility (4). However, the pregnancy rate in patients who undergo ovarian cystectomy is significantly lower, while the recurrence rate of ovarian cysts is significantly higher. Therefore, decisions regarding the surgical treatment of women who desire fertility preservation should be well considered due to the risk of future surgery (5, 6).

Conservative therapy for endometriosis has recently involved the use of gonadotropin-releasing hormone agonists, combined oral contraceptives, danazol, and dienogest (DNG).

DNG is a fourth-generation progestin with potent

* Department of Obstetrics and Gynecology, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Kahoku, Ishikawa 920-0293, Japan
Tel: +81-76-218-8143, Fax: +81-76-286-2629,
E-mail: terry-1@kanazawa-med.ac.jp
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oral pregestational activity that inhibits the clinical symptoms of endometriosis. DNG is a drug that is safe for long-term use as it does not exert androgenic, glucocorticoid, or mineralocorticoid effects (7). Consequently, in this study, we focused on DNG and investigated the effectiveness of conservative DNG treatment in patients with chocolate cysts.

Materials and Methods

This study is a retrospective observational study that was approved by the Kanazawa Medical University Ethics Committee. One hundred fifty-two Japanese patients with endometriosis who were treated with DNG between April 2008 and September 2019 provided informed consent. Exclusion criteria were as follows: participants treated with DNG for fewer than 6 months, patients who received DNG to prevent postoperative recurrence and endometriosis, and patients with endometriosis who did not have chocolate cysts. Forty patients with chocolate cysts who were treated with DNG met the inclusion criteria and were included in the study. The following characteristics were analyzed: ovarian cyst diameter, reduction rate in ovarian cyst diameter, serum cancer antigen 125 (CA125) levels during treatment, and estradiol levels after 6 months of treatment. In addition, we compared the group that achieved a complete (CR) or partial response (PR) after DNG treatment and the group with stable disease (SD) or progressive disease that did not achieve a reduction rate in ovarian cyst diameter.

The degree of ovarian cyst reduction was determined by one-way measurement according to the Response Evaluation Criteria in Solid Tumors criteria. A clinical diagnosis was based on ultrasonography (SONOVISTA FX, Mochida Siemens, Tokyo, Japan) and magnetic resonance imaging (MRI) (MAGNETOM Avanto 1.5T, Siemens, Erlangen, Germany). MRI images were analyzed by multiple radiologists. The Wilcoxon signed-rank test were used to assess differences between two dependent groups. The Mann-Whitney U test and receiver operating characteristic (ROC) curves were used to assess differences between two independent groups. The Spearman correlation analysis were used for correlation analysis. All statistical analyses were performed using GraphPad Prism 6 version 6.05 (GraphPad Software, San Diego, CA, USA). The significance level was set at $P = 0.05$.

Results

Forty women were included in this study. The mean patient age ± the standard deviation was 38.3 ± 7.2 years (range, 24-50 years), while the mean body mass index (BMI) was 22.4 ± 3.9 (range, 15.1-33.1) kg/m^2. All patients with chocolate cysts who received DNG showed significant reductions in ovarian cyst diameter (58.3 ± 26.4 vs 47.6 ± 28.5 mm, $P < 0.001$, Wilcoxon signed-rank test) and CA125 levels during treatment (78.0 ± 102.0 vs 51.9 ± 108.0 U/mL, $P < 0.01$). The estradiol levels in patients with chocolate cysts who received DNG was, on average, 53.9 ± 32.6 pg/mL after 6 months of treatment. Table 1 presents the characteristics of patients who were treated with DNG.

The patients who exhibited the highest ovarian cyst reduction rate had approximately 40-mm-wide ovaries. However, the effect of DNG was decreased among patients with cysts whose diameters ranged from 60 to 70 mm (Figure 1).

The correlation between ovarian cyst diameter and the ovarian cyst reduction rate was analyzed using Spearman correlation analysis. The Spearman correlation coefficient was $r = -0.478$, which indicates a moderate negative correlation (Figure 2).

The Spearman correlation coefficient for the association between ovarian cyst diameter and the reduction rate in CA125 levels was $r = 0.087$ (95% confidence interval (CI), -0.248-0.404; $P = 0.603$), which indicates no significant correlation.

Table 1. Characteristics of patients with chocolate cysts who were treated with dienogest.

Characteristics	n = 40 (mean ± SD, range)
Age (years)	38.3 ± 7.2, 24–50
Body mass index	22.4 ± 3.9, 15.1–33.1
Ovarian cyst diameter (mm)	
Pre-treatment	58.3 ± 26.4, 20.0–156.0
Post-treatment (6 months)	47.6 ± 28.5, 13.7–155.0
CA125 (U/mL)	
Pre-treatment	78.0 ± 102.0, 6.5–621.0
Post-treatment (6 months)	51.9 ± 108.0, 6.0–659.0
Estradiol (pg/mL)	
Post-treatment (6 months)	53.9 ± 32.6, 12.0–142.0
Treatment period (months)	n, %
6–12	15 (37.5)
13–24	1 (2.5)
25–36	6 (15.0)
37–48	7 (17.5)
49–60	2 (5.0)
≥ 61	9 (22.5)
Outcome	n, %
Continued drug treatment	21 (52.5)
Change in drug treatment	3 (7.5)
Discontinuation of drug treatment	4 (10.0)
Surgery	10 (25.0)
Others	2 (5.0)

The Spearman correlation coefficient for the association between the estradiol levels and the ovarian cyst reduction rate was r = 0.244 (95% CI, -0.162-0.579; P = 0.221), which indicates no significant correlation.

The 40 patients exhibited the following treatment responses: 27 patients achieved a PR and 13 patients remained SD. Table 2 presents the comparisons between the group that achieved PR after DNG treatment and the SD group that did not achieve a reduction in ovarian cyst diameter.

A significant difference was observed in the diameter of ovarian cysts between the group that achieved PR after DNG treatment and the SD group that did not achieve a reduction in ovarian cyst diameter (48.1 ± 13.4 mm vs 79.6 ± 33.8 mm, P < 0.001).

According to the ROC curve analysis, the area under the curve was 0.816. With a cutoff value of 55.5 mm for the optimal ovarian cyst diameter (Figure 3).

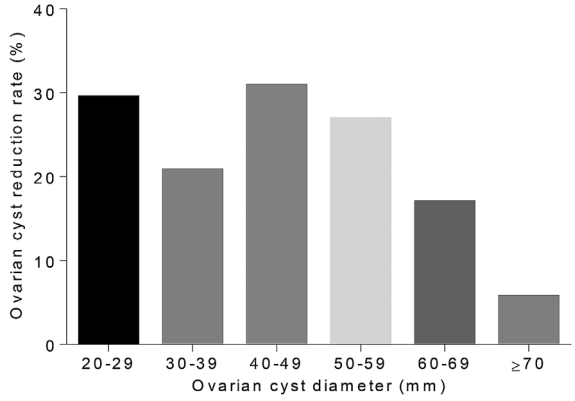

Figure 1. Mean reduction rates among groups with different ovarian cyst diameters.
The ovarian cyst reduction rate was highest in 40-mm-wide ovaries.

Table 2. Comparison of the group that achieved a partial response after dienogest treatment and the group that did not achieve a reduction in ovarian cyst diameter.

Characteristics	Partial response groups (n = 27)	Stable disease groups (n = 13)	P value
Age (years)	38.4 ± 6.3	38.2 ± 9.1	0.759
Body mass index	21.9 ± 3.5	23.4 ± 4.5	0.411
Ovarian cyst diameter (mm) Pre-treatment	48.1 ± 13.4	79.6 ± 33.8	< 0.001*
CA125 (U/mL) Pre-treatment	80.5 ± 116.0	71.9 ± 53.8	0.679
Estradiol (pg/mL) Post-treatment (6 months)	55.6 ± 33.0	46.4 ± 33.0	0.533

* P < 0.001 for the comparison with partial response groups and stable disease groups, according to Mann-Whitney U test.

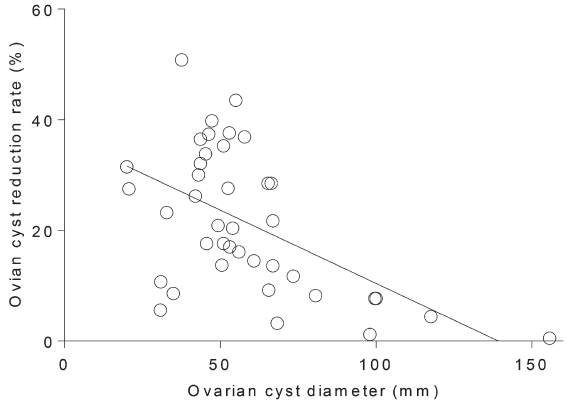

Figure 2. Correlation between ovarian cyst diameter and the ovarian cyst reduction rate.
For the association between ovarian cyst diameter and the ovarian reduction rate, the Spearman correlation coefficient was r = -0.478 (95% confidence interval, -0.693--0.187; P = < 0.01), which indicates a moderate negative correlation.

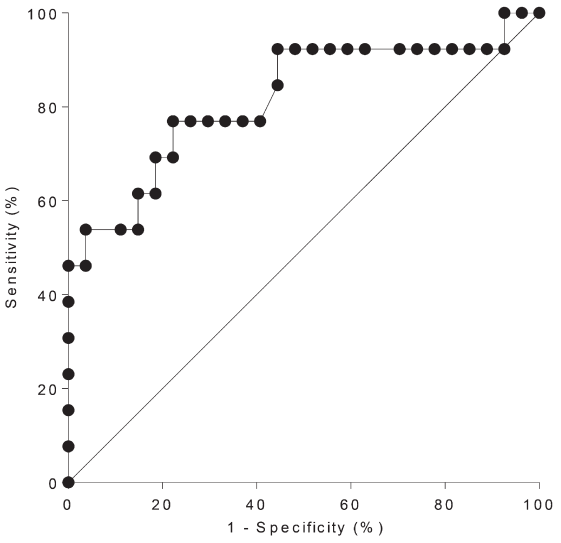

Figure 3. Comparison of the receiver operating characteristic curves between the partial response and stable disease groups after dienogest treatment.
The area under the curve was 0.816 (95% confidence interval, 0.660-0.973). With a cutoff value of 55.5 mm for the optimal ovarian cyst diameter, the sensitivity and specificity were 77.9% and 76.9%, respectively.

Discussion

At our institution, the 40 patients who received DNG showed a significant reduction rate (18.4%) in ovarian cyst diameter before and after treatment ($P < 0.001$). Takenaka et al. reported that the reduction rate of chocolate cysts was 10.2% in 15 patients treated with DNG for 12 weeks (8). Sugimoto et al. reported that the reduction rate in the diameter of chocolate cysts in 26 patients was 27.7% after 15 months of treatment (9). Angioni et al. reported that the average diameter of chocolate cysts in 40 patients who received DNG was 52 ± 22 mm at baseline and 32 ± 12 mm after 6 months of treatment ($P < 0.001$) (10). Consequently, patients with chocolate cysts who receive DNG may be able to avoid surgery while preserving ovarian function, reducing cyst diameter, and improving negative effects on the ovaries.

In patients who received DNG, their ovarian cyst diameter was reduced primarily when their cysts were 40 mm wide. In addition, a moderate negative correlation was observed between the ovarian cyst reduction rate and the ovarian cyst diameter. Normal ovaries are typically 20-30 mm in diameter; thus, chocolate cysts in the 20-30 mm range may introduce a large bias in the cyst reduction rate. It is also likely that the ability of DNG to reduce the diameter of cysts decreases as ovarian cysts continue to grow.

DNG treatment of chocolate cysts resulted in a significant difference between pre- and posttreatment CA125 levels, but no correlation was found between ovarian cyst diameter and the reduction rate in CA125 levels. CA125 is a high-molecular-weight glycoprotein expressed on the surface of cellular derivatives of the embryonic coelomic epithelium. Inflammation that occurs during endometriosis alters endothelial permeability and allows CA125 to enter the circulation (11). Serum concentrations of CA125 rise as endometriosis progresses, and these increases are correlated with the estimated total surface areas of the endometriotic lesions (12). Furthermore, the increase in serum concentrations of CA125 was based primarily on the presence of deeply infiltrative endometriosis and/or endometriomas (13). Thus, improvement of endometriotic lesions decreases CA125 levels. However, improvements in lesions after DNG treatment do not necessarily contribute to a reduction in cyst diameter.

No correlation was observed between estradiol concentrations in the blood and the ovarian cyst reduction rate. Studies have shown that DNG treatment can lead to direct reductions in plasma estradiol levels by induction of ovarian granulosa cell apoptosis. DNG is associated with a relatively moderate inhibition of gonadotropin secretion (14), which leads to a modest reduction in the production of endogenous estradiol. When the estradiol levels are reduced by two different mechanisms, the correlation between the therapeutic effect of DNG and estradiol levels may not be shown.

Of the 40 patients, 27 achieved PR (67.5%) after DNG treatment. To achieve a PR, an average treatment period of 17.3 months was required for patients with chocolate cysts. A significant difference was observed in the degree of reduction between the group that achieved a PR after DNG treatment and the group that did not achieve a reduction in ovary cyst size. Few published articles have focused on the reduction rate of cyst diameter and ovarian cysts during DNG treatment.

Arguments in favor of conservative treatment for DNG highlight the potential malignant transformation of chocolate cysts and their possible recurrence after menopause. A significant number of studies have revealed an increased risk of epithelial ovarian cancer in women with endometriosis, the prevalence of which ranges from 0.7% to 17% among women with endometriosis (15). Recent molecular studies on the mechanisms of ovarian malignant transformation have found connections between endometriosis and ovarian cancer through pathways associated with oxidative stress, inflammation, and hyperestrogenism (16). Currently, the malignant transformation of chocolate cysts is diagnosed by the following methods: MRI, ^{18}F-FDG positron emission tomography/computed tomography, CA125 levels, AT-rich interaction domain 1A gene levels, and heme iron concentrations (17-19). However, conventional tests are often used to diagnose this condition after carcinogenesis, and no early diagnostic marker has been established. Therefore, to preserve chocolate cysts over the long-term, it is recommended that tumor markers be detected and that imaging be performed every few months (20).

The present study has some limitations. The sample size may have been too small; therefore, larger studies are required to confirm these results. Moreover, many of the Japanese patients included in this study already have a low BMI. Therefore, the ovarian reduction rate may be different in Western women.

In conclusion, DNG may be considered as a long-term preservation therapy because chocolate cysts smaller than 60 mm may decrease, resulting in a PR. However, chocolate cysts larger than 60 mm that are treated with DNG do not sufficiently shrink, and surgical treatment is recommended for patients who do not desire fertility preservation. In addition, we plan to perform a large prospective study on the conservative treatment of patients with chocolate cysts.

Conflicts of interest statement

The authors declare no conflict of interest associated with this manuscript.

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